REMARKS

Amendments

Claims 1-28 have been canceled, claims 29, 33 and 36 have been amended, and claims 40 and 41 have been added. Upon entry of the amendment, claims 29-36 and 38-41 will be pending. Support for the added claims can be found in the specification, and in the claims as originally filed. The specification has been amended to update priority application information.

The foregoing amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. The Applicant reserves the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

Rejections

Rejections under 35 U.S.C. § 101/112 1st paragraph

The Examiner has rejected claims 29-36, 38 and 39 because the claimed invention is allegedly not supported by either a specific or substantial asserted utility or a well-established utility.

Applicant respectfully traverses the rejection. According to 35 U.S.C. § 101, "[w]hoever invents . . . any new and useful . . . composition of matter may obtain a patent therefore. . . . "

Under the Patent Office's Utility Requirement Guidelines:

> If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.
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> If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.

(emphasis added)(MPEP § 2107, II (A)(3); II (B)(1)). Thus, according to Patent Office guidelines, a rejection for lack of utility may not be imposed where an invention has a well-established utility or is useful for any particular practical purpose. The present invention satisfies either standard.

The present invention has a well-established utility since a person of ordinary skill in the art "would immediately appreciate why" knockout mice are useful. As a general principle, any knockout mouse has the inherent and well-established utility of defining the function and role of the disrupted target gene, regardless of whether the inventor has described any specific phenotypes, characterizations or properties of the knockout mouse. The sequencing of the human genome has produced countless genes whose function has yet to be determined. According to the National Institute of Health, knockout mice represent a critical tool in studying gene function:

> Over the past century, the mouse has developed into the premier mammalian model system for genetic research. Scientists from a wide range of biomedical fields have gravitated to the mouse because of its close genetic and physiological similarities to humans, as well as the ease with which its genome can be manipulated and analyzed.
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> In recent decades, researchers have utilized an array of innovative genetic technologies to produce custom-made mouse models for a wide array of specific diseases, as well as to study the function of targeted genes. One of the most important advances has been the ability to create transgenic mice, in which a new gene is inserted into the animal's germline. Even more powerful approaches, dependent on homologous recombination, have permitted the development of tools to "knock out" genes, which involves replacing existing genes with altered versions; or to "knock in" genes, which involves altering a mouse gene in its natural location. To preserve these extremely valuable strains of mice and to assist in the propagation of strains with poor reproduction, researchers have taken advantage of state-of-the-art reproductive technologies, including cryopreservation of embryos, in vitro fertilization and ovary transplantation.

(http://www.genome.gov/pfv.cfm?pageid=10005834) (emphasis added). Thus, the knockout mouse has been accepted by the NIH as the premier model for determining gene function, a utility that is specific, substantial and credible.

Knockout mice may be used as research tools, with respect to which the Patent Office has commented:

> Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

(MPEP § 2107.01, I). As with gas chromatographs, screening assays and nucleotide sequencing techniques, knockout mice have a clear, specific and unquestionable utility (e.g., they are useful in analyzing gene function).

According to the Molecular Biology of the Cell (Albert, 4th ed., Garland Science (2002)), one of the leading textbooks in the field of molecular biology:

> Extensive collaborative efforts are underway to generate comprehensive libraries of mutation in several model organisms including . . . the mouse. The ultimate goal in each case is to produce a collection of mutant strains in which every gene in the organism has either been systematically deleted, or altered such that it can be conditionally disrupted. Collections of this type will provide an invaluable tool for investigating gene function on a genomic scale.

(p. 543)(emphasis added).

According to Genes VII (Lewin, Oxford University Press (2000)), another well respected textbook in the field of genetics:

> The converse of the introduction of new genes is the ability to disrupt specific endogenous genes. Additional DNA can be introduced within a gene to prevent its expression and to generate a null allele. Breeding from an animal with a null allele can generate a homozygous "knockout", which has no active copy of the gene. This is a powerful method to investigate directly the importance and function of the gene.

(p. 508)(emphasis added).

Applicant submits that since one of ordinary skill in the art would immediately recognize the utility of a knockout mouse in studying gene function, a utility which is specific, substantial

and credible, the invention has a well-established utility, thus satisfying the utility requirement of section 101. On this basis alone, withdrawal of the rejection with respect to the present invention is warranted, and respectfully requested.

In addition, the claimed invention is useful for a particular purpose. The claimed mice exhibit increased seizure susceptibility, increased glucose tolerance, and/or increased ability to metabolize glucose, and the female mice have exhibited increased body weight, increased body length and increased body weight to body length ratio. One of skill in the art would recognize that these mice are useful for studying the association of the CX2 gene with any one of these phenotypes.

For example, Wang et al. (Surgery (2004) 136(3):585-92) studied glucose tolerance in SSTR1/SSTR5 double knockout mice:

> Previous studies conducted in our laboratory showed that single-gene ablation of somatostatin receptor (SSTR)1 or 5 results in diabetes in mice. The objective of this study was to determine the effect of double-gene ablation of SSTR1 and SSTR5 on insulin secretion and glucose homeostasis in mice. METHODS: SSTR1/5 -/- mice and wild-type (WT) control mice were generated and their genotype verified via polymerase chain reaction. Insulin secretion and glucose levels in these mice were examined with the use of an intraperitoneal glucose tolerance test (1.2-2.0 g/kg body weight). In vitro glucose-stimulated insulin secretion was studied with the use of the isolated perfused mouse pancreas model and islet culture techniques. Pancreata morphologic alterations were determined, and an immunohistochemistry analysis was performed. RESULTS: In vitro incubation of isolated islets from WT mice with somatostatin peptides resulted in significant reduction in insulin secretion, whereas SSTR1/5 -/- mouse islets had no response to somatostatin peptides confirming SSTR1/5 gene ablation. SSTR1/5 -/- mice also had significant increase of both basal and glucose-stimulated insulin levels in vitro. During the intraperitoneal glucose tolerance test, SSTR1/5 -/- mice had significantly improved glucose tolerance and sustained an increase in late-phase insulin secretion in vivo. Histological analysis demonstrated significant islet hyperplasia in the SSTR 1/5 -/- mouse pancreas. Immunostaining revealed an overall increase of glucagon and pancreatic polypeptide-producing cells in the islets of SSTR1/5 -/- mice. CONCLUSIONS: Double-gene ablation of SSTR1 and SSTR5 in mice resulted in a distinct phenotype with islet cell hyperplasia, hyperinsulinemia, and improved glucose tolerance. This form of diabetes differs from that seen in mice in which only the SSTR1 or SSTR5 gene was ablated. These results demonstrate that SSTR1 and SSTR5 are important regulators of insulin secretion and glucose regulation, and suggest that SSTR1 and SSTR5 are coordinately regulated.

(emphasis added)(abstract)

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15349106).

Thus, one of skill in the art, such as Wang, would clearly accept that the asserted utility is credible.

The Examiner argues that the prior art does not teach the genotypic-phenotypic association of the CX2 receptor and the disclosed phenotype is correlated with any specific disease. The Examiner's arguments are similar to arguments made by the Patent Office with respect to pharmaceutical compounds the utility of which were based on murine model data, arguments which were dismissed by the Federal Circuit in *In re Brana* (34 U.S.P.Q.2d 1436)(Fed. Cir. 1995). The case involved compounds that were disclosed to be effective as anti-tumor agents and had demonstrated activity against murine lymphocytic leukemias implanted in mice. The court ruled that the PTO had improperly rejected, for lack of utility, claims for pharmaceutical compounds used in cancer treatment in humans, since neither the nature of invention nor evidence proferred by the PTO would cause one of ordinary skill in art to reasonably doubt the asserted utility.

The first basis for the Board's holding of lack of utility (the Board adopted the examiner's reasoning without any additional independent analysis) was that the specification failed to describe any specific disease against which the claimed compounds were useful, and therefore, absent undue experimentation, one of ordinary skill in the art was precluded from using the invention. (*In re Brana* at 1439-40). The Federal Circuit reasoned that the leukemia cell lines were originally derived from lymphocytic leukemias in mice and therefore represented actual specific lymphocytic tumors. The court concluded that the mouse tumor models represented a specific disease against which the claimed compounds were alleged to be effective. (*In re Brana* at 1440).

The Board's second basis was that even if the specification did allege a specific use, the applicants failed to prove that the claimed compounds were useful.

The Federal Circuit responded: "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of Section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (*Brana* at 1441, *citing In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971)). From this it followed that the PTO has the initial burden of

challenging a presumptively correct assertion of utility in the disclosure. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. (*Id.*)

The court held that the Patent Office had not met its burden. The references cited by the Board did not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, the references merely discussed the therapeutic predictive value of *in vivo* murine tests -- relevant only if the applicants were required to prove the ultimate value in humans of their asserted utility. The court did not find that the nature of the invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness. The purpose of treating cancer with chemical compounds did not suggest an inherently unbelievable undertaking or involve implausible scientific principles. (*Id.*)

The Court concluded that one skilled in the art would be without basis to reasonably doubt the asserted utility on its face. The PTO had not satisfied its initial burden. Accordingly, the applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of Section 112. (*Id.*)

As in *Brana*, Applicant has asserted that the claimed invention is useful for a particular practical purpose, an assertion that would be considered credible by a person of ordinary skill in the art. As discussed above, the claimed mice have demonstrated increased seizure susceptibility. The acceptance among those of skill in the art of knockout mice demonstrating such properties is clearly demonstrated by, for example, the Prosser reference cited above.

Whether the specification discloses a link between these particular phenotypes and the gene in mice and humans is not relevant to whether the claimed invention satisfies the utility requirement. It is enough that knockout mice are recognized in the art as models for determining gene function. Moreover, the tests used by Applicant to determine the asserted phenotype are well recognized by those skilled in the art. In *Brana*, the claimed compound had demonstrated activity against a murine tumor implanted in a mouse. Yet, the Federal Circuit found that utility had been demonstrated. Here, the invention relates to a disruption in a murine gene in a mouse. Like the tumor mouse model, the knockout mouse with a specific gene disrupted is a widely accepted model, the utility of which would be readily accepted in the art. It is submitted that one

skilled in the art would be without basis to be reasonably doubt Applicant's asserted utility, and therefore the Examiner has not satisfied the initial burden.

The Examiner further argues that the cited phenotypes of increased body weight, increased body length and increased body and length ratio are not credible, citing Figure 3.

Applicant disagrees. The specification clearly states that these phenotypes were observed in female mice (see Example 1). Figure 3 is representative of male mice (see Example 3). The claims have been amended to clarify the distinction.

In summary, Applicant submits that the claimed transgenic mouse, regardless of any disclosed phenotypes, has inherent and well-established utility in the study of the function of the gene, and thus satisfies the utility requirement of section 101. Moreover, Applicant believes that the transgenic mice are useful for studying CX2 gene function with respect to the cited phenotypes and are therefore useful for a specific practical purpose that would be readily understood by and considered credible by one of ordinary skill in the art.

In light of the arguments set forth above, Applicant does not believe that the Examiner has properly established a *prima facie* showing that establishes that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the Applicant would be specific and substantial. (*In re Brana*; MPEP § 2107).

Withdrawal of the rejections is respectfully requested.

Rejections under 35 U.S.C. § 112, 1st paragraph

Claims 29-36, 38 and 39 have been rejected for lack of enablement, as the claimed invention allegedly lack utility. As set forth above, it the Applicant's position the claimed invention satisfies the utility requirement and therefore one skilled in the art would clearly know how to use the invention.

The Examiner argues that the phenotype of a knockout animal is highly unpredictable, and that the phenotype is affected by genetic background.

Applicant disagrees. The data set forth in the specification is based on the use of age, gender and strain matched controls. The pathologists conducting the phenotypic analyses are highly skilled in their art. Genetic, background and strain variances were taken into account when reaching their conclusions with respect to phenotyping the claimed mice.

The Examiner argues that one skilled in the art would not know how to use a heterozygous mouse without a phenotype. Applicant disagrees. Heterozygous mice are used to breed the homozygous mice, and in fact are preferred by Assignee Deltagen's customers. Moreover, the heterozygous mice comprise a visible marker, a gene encoding lacZ. These mice are useful for studying gene expression patterns (see Example 2).

The Examiner argues that the state of the art considers generating null mutations in mice and the resulting phenotypic behavior as unpredictable. Again, the analyses performed and described in the specification utilized age, gender and strain matched controls. Crawley (published in 1997), cited by the Examiner, addresses possible strain variations, but also teaches how to take such variations into account when generating knockouts. It should be also noted that Crawley acknowledges the utility of knockout mice:

> Using the referenced information, molecular geneticists can choose optimal parental strains of mice, and perhaps develop new embryonic stem cell progenitors, for new knockouts and transgenics to investigate gene function, and to serve as animal models in the development of novel therapeutics for human diseases.

(abstract).

The present specification is enabling for the claimed invention as it teaches one how to make a mouse having the recited phenotypes. If another made a CX2 deficient mouse without the cited phenotypes, it would be outside the scope of the claims. Withdrawal of the rejections is respectfully requested.

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. **13-2725**.

Respectfully submitted,

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Date

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